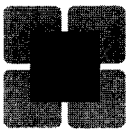

Serum lipoprotein levels fail to predict postangioplasty recurrent coronary artery stenosis

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■ A prospective study to explore the role of serum lipoproteins in the development of recurrent stenosis after percutaneous transluminal coronary angioplasty was conducted on serum samples from 103 patients. Serum was collected at the time of angioplasty and evaluated for total cholesterol, total triglycerides (TG), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein cholesterol, and apolipoproteins A1 and B. In addition, LDL cholesterol/HDL cholesterol ratios and apolipoprotein B/A1 ratios were calculated for each sample. Information was then gathered from four years of follow-up after angioplasty, which was sufficient to establish the presence or absence of recurrent stenosis in 87 patients (68 males and 19 females). Stenosis recurred in 31 of the 87 patients (36%); the rate was similar for males (35%) and females (37%). Univariate analysis of the total patient population revealed no statistically significant difference in values for any of these lipoprotein parameters between success and recurrence groups. Likewise, multivariate analysis revealed no combination of lipoprotein values to be associated with success or recurrence. Findings were similar for the males alone and the total group of males and females. The female group was too small for separate statistical analysis. The power of this study to detect meaningful differences in each of these parameters except TG was at least 80%. These results do not support the hypothesis that lipoprotein factors influence the development of recurrent stenosis in patients undergoing coronary angioplasty.

□INDEX TERMS: ANGIOPLASTY, TRANSLUMINAL; LIPOPROTEINS □CLEVE CLIN J MED 1989; 56:509–514

PERCUTANEOUS transluminal coronary angioplasty (PTCA) is a well-established technique for treating coronary atherosclerosis.[1] However, recurrent coronary artery stenosis occurs in about one third of all patients undergoing angioplasty and remains the principal problem with this technique.[2] Evidence from an autopsy study indicates that restenosis is due to proliferation of intimal and medial smooth muscle cells, induced by trauma to the vessel wall at the time of angioplasty.[3] While the factors determining which patients will develop recurrent stenosis remain unclear, lipoproteins have been considered likely contributors to this process.

In a recent study, we looked for associations between a number of routinely ordered laboratory tests and the development of recurrent stenosis.[4] We found that none of the factors examined (except cholesterol in a sub-

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TABLE 1
LABORATORY TEST RESULTS IN TOTAL SUCCESS AND RECURRENCE GROUPS

Test	Patient group	Number of patients	Mean	SD	P
Cholesterol	success	56	5.917 (228.8)	1.386 (53.6)	.642
mmol/L (mg/dL)	recurrence	31	5.790 (223.9)	1.133 (43.8)	
Triglycerides	success	56	1.941 (171.9)	0.930 (82.4)	.251
mmol/L (mg/dL)	recurrence	31	2.253 (199.6)	1.604 (142.1)*	
HDL cholesterol	success	56	0.962 (37.2)	0.266 (10.3)	.945
mmol/L (mg/dL)	recurrence	31	0.959 (37.1)	0.305 (11.8)	
LDL cholesterol	success	56	3.907 (151.1)	1.065 (41.2)	.756
mmol/L (mg/dL)	recurrence	30†	3.988 (154.2)	1.241 (48.0)	
VLDL cholesterol	success	56	0.890 (34.4)	0.425 (16.4)	.676
mmol/L (mg/dL)	recurrence	30†	0.934 (36.1)	0.517 (20.0)	
Apoliprotein A1	success	56	1.266 (126.6)	0.217 (21.7)	.844
g/L (mg/dL)	recurrence	31	1.276 (127.6)	0.237 (23.7)	
Apoliprotein B	success	56	0.885 (88.5)	0.151 (15.1)	.458
g/L (mg/dL)	recurrence	31	0.915 (91.5)	0.228 (22.8)	
LDLC/HDLC	success	56	4.23	1.31	.523
	recurrence	30†	4.45	1.76	
Apo B/Apo A1	success	56	0.721	0.186	.451
	recurrence	31	0.760	0.296	

* Excluding the one patient with triglycerides of 8.479 mmol/L (751 mg/dL), the mean triglycerides concentration for the 30 remaining patients in the recurrence group was 2.020 mmol/L (178.9 mg/dL) and the SD is 1.169 mmol/L (103.5 mg/dL).
† These parameters were not calculated for the one patient with triglycerides of 8.479 mmol/L (751 mg/dL).

group of women) was a statistically significant predictor for the condition. However, lipoprotein levels other than total cholesterol (TC) were not available for examination. Therefore, a prospective study in which lipoprotein assays were performed on serum obtained from angioplasty patients was conducted to assess the role of lipoproteins in the development of recurrent stenosis.

MATERIALS AND METHODS

Patients who underwent coronary angioplasty performed by Drs. Hollman and Meir between November 18, 1982, and March 6, 1983, at Emory University Hospital, Atlanta, were eligible for the study. These investigators performed slightly more than one-third of all the angioplasties done at Emory during that period. Assignment of angioplasty cases to the cardiologists on the service was on a rotational basis and was independent of patient characteristics.

One hundred three patients were studied. This population represented approximately 70% of the patients treated by the investigators. Blood samples from the remaining patients could not be obtained or expeditiously processed because of logistical reasons unrelated to patient characteristics.

Adequate follow-up information was available on 87 of the 103 patients. The follow-up period for all patients has been at least four years. In 74 cases, classification into success or recurrence groups was on the basis of follow-up angiography including all the recurrences and in 13 cases on the basis of clinical information including treadmill testing. Treadmill testing is a highly sensitive means of determining recurrent stenosis, particularly in patients who have had multiple stress tests in the past (as was the case with our patients) and has been used by other groups of investigators.[5,6]

Protocol for patients undergoing angioplasty

Coronary angioplasty was performed as described by Grüntzig et al.[1] Patients arrived in the hospital on the evening before angioplasty and were given aspirin (650 mg). Angioplasty was performed the following day.

Patients received aspirin therapy for six months following angioplasty. Follow-up angiography was performed at the onset of recurrent symptoms or at six months following angioplasty if the patient remained asymptomatic. In some of the asymptomatic patients, only a clinical examination including a treadmill test was done. If the examination was normal, the patient was classified as a continuing success. All patients had either a treadmill test or underwent angiography approximately six months after angioplasty. Patients were subsequently followed with clinical examinations and stress tests at intervals, and in some cases, further angiography. The status of all patients was reviewed and updated four years after angioplasty.

Recurrent stenosis was defined as a 50% loss of the gain in luminal diameter initially obtained at angioplasty. Thus, if a patient's narrowing of luminal diameter was 80% before PTCA and 20% immediately after PTCA, then a subsequent narrowing of 50% or greater in luminal diameter was termed a recurrence. Patients in whom recurrent stenosis did not develop were termed successes. Initial and follow-up angiograms were measured in one to four non-overlapping views using a digital caliper (A2D cinematic viewer and Prodical 1101 Programmable Digital Caliper, Ultrasound, Inc., Killingsworth, Conn.). Results of follow-up angiograms not performed at Emory University Hospital were mailed to Emory University for evaluation. Where follow-up angiography

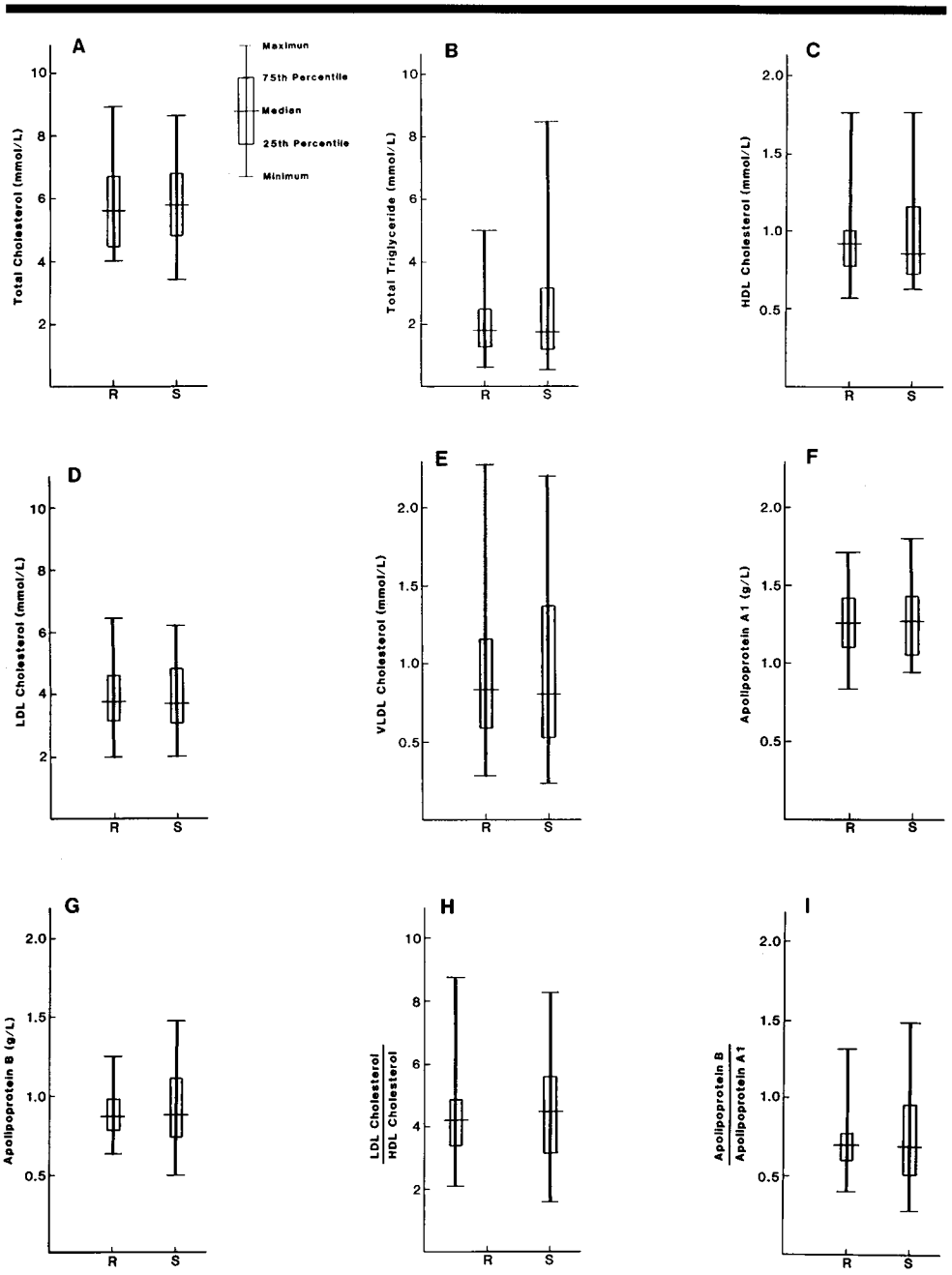

FIGURE 1. Box-and-whisker plots of lipoprotein test results in success and recurrent stenosis patients. FIGURE 1A. TC. FIGURE 1B. TG. FIGURE 1C. HDL cholesterol. FIGURE 1D. LDL cholesterol. FIGURE 1E. VLDL cholesterol. FIGURE 1F. Apo A1. FIGURE 1G. Apo B. FIGURE 1H. LDL cholesterol/HDL cholesterol ratio. FIGURE 1I. Apo B/apo A1 ratio. *S* = success group; *R* = recurrence group.

was available, recurrence was diagnosed solely on the basis of angiographic criteria, independent of a patient's symptoms and functional class. In the cases in which late angiography was unavailable, the diagnosis of success was based upon the absence of clinical symptoms or signs of restenosis for four years following angioplasty, together with a normal treadmill test.

Blood samples for lipoprotein analysis were obtained directly from the femoral vein at the time of angioplasty. Samples were immediately placed on ice, and serum was obtained by centrifugation within 30 minutes. Serum specimens were aliquotted into multiple fractions which were frozen at -80°C until assayed. All patients were hospitalized and fasted overnight prior to angioplasty.

Laboratory tests

The following laboratory tests were performed on serum samples obtained during angioplasty: TC, total triglycerides (TG), high-density lipoprotein (HDL) cholesterol, apolipoprotein A1 (apo A1), and apolipoprotein B (apo B). In addition, very low-density lipoprotein (VLDL) cholesterol and low-density lipoprotein (LDL) cholesterol were calculated according to the widely employed formula established and validated by Friedewald et al.[7] Specifically, VLDL = TG (except for markedly elevated triglycerides) and LDL = TC – HDL – VLDL. In the one case where TG was extremely elevated (8.479 mmol/L, 751 mg/dL), LDL and VLDL were not calculated. Apo A1 assays were performed as described by Austin and Maznicki.[8] Apo B assays were performed on the COBAS-BIO centrifugal analyzer (Roche Analytical Instruments, Inc., Nutley, NJ) using reagents purchased from Calbiochem-Behring Corp., LaJolla, Calif. Apolipoprotein assays were standardized using control material obtained from the Centers for Disease Control, Atlanta. Ratios of LDL/HDL and apo B/apo A1 were also calculated for all patients. All laboratory tests were performed in the clinical laboratories of Emory University Hospital, Atlanta.

Statistical analysis

Univariate analysis was performed to determine the effect of each laboratory parameter on recurrence rate. Student's *t* test was employed to compare the mean values of the parameters in the success and recurrence groups.

A stepwise multiple logistic regressive analysis[9] was employed to examine the possibility that some combination of the individual laboratory tests would distinguish between the success and recurrence groups.

In addition, the power of the study was assessed by determining for each parameter the differences in mean values for the two groups that could be detected with a power of 80%, given the sample sizes and standard deviations in this study. A power of 80% is generally considered adequate for such studies.[10]

RESULTS

The overall stenosis recurrence rate was 36% (31 of 87 patients). The rate for men was 35% (24 of 68 patients); for women, 37% (7 of 19 patients). Recurrence rates for patients treated more recently at Emory University Hospital are slightly lower.[6] The statistical treatment of individual laboratory test results was carried out only for the total group (men and women) and for men alone since the women group was too small for separate analysis, although the results for women were qualitatively similar to those for men. Because the results for men alone were essentially identical with those for the total group, only the data for the total group will be presented in detail here.

Univariate analysis of laboratory test results

Results of univariate analysis for the sucess and recurrence groups are shown in *Table 1* and *Figure 1*. *Table 1* provides the mean values and standard deviations as well as the *P* value for comparing the mean values of each of the laboratory tests in the success and recurrence groups. *Figure 1* provides comparative information on median, 25th and 75th percentile, and range for all test results in both groups. No significant differences in the mean values of the success and recurrence groups were found. Likewise, only minor differences in ranges or 25th or 75th percentiles were noted for the various parameters under study. Even factors that are highly correlated with rates of atherosclerotic heart disease, such as LDL and HDL and the apolipoproteins, showed no differences in mean values between success and recurrence groups. Likewise, neither the LDL/HDL ratio nor the apo B/apo A1 ratio showed any correlation with recurrence. No significant differences in laboratory test results were observed between the 43 success patients who underwent follow-up angiography and the 13 cases whose diagnosis of success was based upon clinical findings and a negative treadmill test.

Multiple logistic regression analysis

Multiple logistic regression analysis was performed to determine if any combination of the above parameters was associated with recurrence. No statistically significant differences in test values were found for results of

any combination of these tests (including calculated parameters and ratios).

Estimation of the power of this study to detect significant associations between lipoprotein parameters and recurrence

For each parameter, we determined the difference between the mean values of the success and recurrence groups that could be detected with 80% power using our samples. The results are: TC, 0.776 mmol/L (30 mg/dL); TG, 0.632 mmol/L (56 mg/dL); HDL cholesterol, 0.181 mmol/L (7 mg/dL); LDL cholesterol, 0.698 mmol/L (27 mg/dL); VLDL cholesterol, 0.284 mmol/L (11 mg/dL); apo A1, 0.15 g/L (15 mg/dL); and apo B, 0.11 g/L (11 mg/dL). Based upon these findings, there was a reasonable chance (80%) of detecting clinically meaningful differences (should they have existed) for all parameters under study except TG, for which the value of 0.632 mmol/L is higher than desirable. The large standard deviation for triglyceride levels, particularly in the recurrence group, accounted for this high value.

DISCUSSION

The cause of recurrent stenosis after angioplasty remains unknown. Our previously reported autopsy studies suggest that the anatomic basis of recurrent stenosis consists of an intimal proliferation of myofibroblasts, along with deposition of collagen, which leads to luminal narrowing that, in some cases, may be concentric.[3] Because of the importance of lipoproteins in the pathogenesis of coronary atherosclerosis, consideration has been given to the possibility that these factors are important in the development of recurrent coronary artery stenosis following angioplasty.

In a recently reported study,[4] we examined the potential value of a number of common clinical laboratory tests in predicting recurrent stenosis. A statistical association between serum cholesterol and recurrence was reported, but only for a subgroup of women receiving aspirin after angioplasty and not for either the total group of women, the total group of men, or the men receiving aspirin. Because of the large number of parameters examined, it could not be ruled out that this association occurred by chance. Hence, it was important to extend those preliminary findings by carrying out a prospective study in which a fairly complete battery of lipoprotein tests was examined.

The present study, which fulfills that need, provides strong evidence that serum lipoprotein concentrations do not play a major role in the development of recurrent stenosis after PTCA. The major lipid and apolipoprotein fractions that correlate with the development of coronary atherosclerosis were examined, and none of them showed any association with recurrent stenosis. Our previous anatomic studies of recurrent stenosis after coronary angioplasty concur with these findings in that they showed deposition of apolipoproteins in old atherosclerotic plaque but none in the newly deposited fibroblastic tissue at the site of the restenosis.[3]

Although the present study deals with the effect on recurrence of lipid levels at the time of angioplasty, it does not directly address the question of whether lowering serum lipid concentrations after angioplasty might reduce the incidence of recurrence. The patients in our study were all given dietary advice, but there was no systematic attempt to modify their lipid levels following angioplasty. Future studies are planned in which lipid levels will be monitored during the six-month healing period after angioplasty in order to shed further light on this question.

While the number of patients in the present investigation was less than 100, the power of our study was adequate to detect clinically meaningful differences in the various parameters, with the exception of triglycerides. In the case of that parameter, large differences between success and recurrence groups could be ruled out, but smaller differences of up to about 0.55 mmol/L (50 mg/dL) could have been missed. Additional studies to clarify this point would be appropriate.

Our conclusions apply primarily to men, since the number of woman patients was too small for separate statistical evaluation. Further work to evaluate the effects of lipoproteins on restenosis rates in women may be indicated. However, the present results, together with the available anatomic information, suggest that future investigations of factors involved in restenosis may more profitably be directed toward other areas, such as thrombosis, platelet activation, and the myofibroblastic reparative response.

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